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EXAMINER	
EINSMANN, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,323	YOSHIDA ET AL.	
	Examiner	Art Unit	
	Juliet C Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 9/19/02, paper number 7. Claims 4 to 9 have been amended and claims 10-15 have been added. Claims 4-15 are pending. Applicant's amendments and arguments have been thoroughly reviewed. Any rejections not reiterated in this action have been withdrawn. New grounds of rejection are set forth. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

2. The drawings submitted as Figures 4, 5, 6, and 8 are not acceptable for examination because the drawings are illegible. New drawings are required.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to

be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in this Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Claim Rejections - 35 USC § 112

3. Claims 4-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "DNA data containing medium" in claims 4-15 appears to represent new matter. The response asserts that basis for this limitation is found in the specification for example on page 10, line 14 to page 12, line 3 (page 5 of the response). However, this recitation in the specification merely contains information about a method for the practice of a genomic DNA analysis method. The specification does not refer to or define products that are DNA data containing mediums. Thus, the limitation is rejected as being new matter.

Furthermore, in claim 7, the limitation "comprises a recognition sequence that includes **at least one** N" is not supported by the specification. The specification teaches that the restriction enzyme BstXI "is a 3' protruding type and has N in its recognition sequence," and also provides

a list of other restriction enzymes that may be useful in the disclosed methods. BstXI has 6 "N's" in its recognition sequence. Of the restriction enzymes listed in the specification as being useful in the claimed methods, not a single one contains only one "N" in the recognition sequence. Thus, the specification does not explicitly or implicitly provide basis for a genus of restriction enzymes that contain "at least one N."

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 4-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-15 are indefinite because, while the preamble of the claims sets for a genomic DNA containing medium obtained by a particular method, yet the method is not directed towards the production of a product. The specification does not provide any definition of the claimed "DNA containing medium." The final process step of the recited methods is "detecting the spots of labeled DNA fragments" or "comparing the resulting spots" and thus, the claimed product is undefined. It is not clear if the claimed product is meant to be, for example a gel which contains DNA that was analyzed by the method, or a computer that contains information about such a gel, or any product that was produced during the recitation of the method steps- for example, the treated genomic DNA produced in step (a), since the method recited as the process for making the claimed products is not a process of making itself. While claim 9 does recite that the DNA data containing medium comprises an electrophoresis gel, it is unclear how this recitation relates

to claims 8 and 4 from which claim 9 depends, since none of these previously recite a gel or a method of making a gel. The metes and bounds of the claimed products are unclear and should be clarified.

Further, the method steps themselves are indefinite. In claims 4, 10, and 12 the recitation "which is cut by the first restriction enzyme" in step (b) is unclear because it is not clear if this step directs a second cutting step with the first restriction enzyme or if this recitation is merely indicating that the restriction cleavage site was already cut by the enzyme. Amendment of the claim to read "which was cut" will clarify this matter.

In claims 4, 10, and 12, steps (c) and (d), it is not clear how treating the DNA fragments with restriction enzymes results in fractionations that have dimension (i.e. first or second dimensional fractionation). Cleaving with restriction enzymes will result in cut DNAs in solution, and it is not clear from the claims how these have dimension.

In step (e) of claims 4 and 12, the recitation "the spots" and in step (e) of claim 10 the recitation "the resulting spots" lack proper antecedent basis because the claims do not previously refer to spots. The fractionation step of (d) only to requires treating the DNA fragments with a third restriction enzyme.

Claim 9 is indefinite because the claim recites that the medium comprises an electrophoresis gel, yet the process for producing the DNA data containing medium recited in claim 4 is not directed towards the production of a gel (or any other particular product, for that matter). Thus, it is not clear how the gel recited in claim 9 relates to the method of producing the electrophoresis gel recited in claim 9.

Claim 13 is indefinite because it is not clear how the genomic data medium itself can carry out the method step listed in the claim. It would be clearer to write "further comprising adapters have labeled bases attached to the open end of the adapter," or similar language.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 4-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to a genomic DNA data containing medium obtained by the recited methodology, however, neither the claims nor the specification provide any structural information about the claimed medium. That is the claims do not describe what structural characteristics the medium must have, and the method of obtaining the medium does not appear to result in the production of any particular product since the recited methods end with steps of "detecting" or "comparing." Clarification is required.

Prior Art Rejections

8. The claims are drawn to DNA data containing mediums that are obtained by means of a recited method of analysis. Thus, the claims are product by process type claims. It is noted that

product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps (see MPEP 2113). In the instant case, it is difficult to determine the structure implied by the steps because the claims are indefinite and lack written description which provides such structure. None the less, in the interest of compact prosecution, art rejections are set forth.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 4, 5, and 10 rejected under 35 U.S.C. 102(e) as being anticipated by Belyavsky et al. (US 5814445).

This rejection applies to claims 4, 5, and 10 when they are interpreted such that the DNA data containing medium is a gel which contain DNA fragments that were treated as recited in the claims. Belyavsky et al. teach an electrophoresis gel that has thereon nucleic acids that were cut by a restriction enzyme, labeled with an adaptor, and cut twice more with restriction enzymes (see example, Col. 7-9). Furthermore, Belyavsky et al. teach electrophoresis gels wherein the cut DNA is run on an electrophoresis gel via a two-dimensional electrophroesis (see Figure 1). Thus, the teachings of Belyavsky et al. anticipate the instant claims.

It is noted that the methods of Belyavsky et al. are undertaken using cDNA, while the methods of the instant claims recite "genomic DNA." However, this recitation does not place a structural limitation on the claims because cleaved DNA is cleaved DNA and is indistinguishable on an electrophoretic gel. Furthermore, the cDNAs are identical to portions of the genomic DNA of the organism from which they were taken.

11. Claims 4-6 and 12-15 rejected under 35 U.S.C. 102(b) as being anticipated by Hatada *et al.* (PNAS USA, 88, p. 9523-9527).

The instant rejection applies when the "DNA data containing medium" is interpreted to be a computer disk or memory device that contains information genomic DNA that has been treated according to the methods recited in the claims. Hatada et al. provide such a medium, as they teach that a DNA containing medium that was obtained by means of a method of analysis comprising:

(a) treating genomic DNA with a first restriction enzyme (MluI) which is capable of cutting the genomic DNA so that the 3' end of the recognition site has a protruding sticky end

(b) labeling the cleavage site

(c) treating the resulting DNA fragments with a second restriction enzyme to bring about first-dimensional fractionation

(d) treating the fractionated DNA fragments of step (c) with a third restriction enzyme to bring about second-dimensional fractionation; and

(e) detecting the spots of the labeled DNA fragments fractionated in step (d) (Hatada *et al.* describes method p. 9523, Col. 2 thru p. 9524, Col. 1).

Hatada *et al.* teach that one advantage of their method is that the scanning field of the method can be extended by the use of different kinds of landmarks (the first restriction enzyme) and further suggest the use of rare cutting enzymes (p. 9525, Col. 2). Hatada *et al.* provide examples of such enzymes, such as BssHII, an enzyme with a six nucleotide recognition site.

The detection step (e) is carried out using PDQUEST which is a system that scans the electrophoretic gels to produce a computer image, and thus, a genomic DNA data containing medium. It is noted that Hatada et al. do not teach a method that is identical to the method recited in the instantly rejected claims, however, the image that is obtained by the computer, and thus the DNA data containing medium, would not be structurally different in the case of the data image that is obtained.

12. Claims 4-5 and 10-11 rejected under 35 U.S.C. 102(b) as being anticipated by Hayashizaki et al. (Electrophoresis, 1993, 14, 251-258).

The instant rejection applies when the "DNA data containing medium" is interpreted to be a computer disk or memory device that contains information genomic DNA that has been treated according to the methods recited in the claims. Hayashizaki et al. provide such a medium, as they teach that a DNA containing medium that was obtained by means of a method of analysis comprising:

(a) treating genomic DNA with a first restriction enzyme that is sensitive to methylation of the genomic DNA (for example NotI)

(b) labeling the cleavage site

(c) treating the resulting DNA fragments with a second restriction enzyme to bring about first-dimensional fractionation

(d) treating the fractionated DNA fragments of step (c) with a third restriction enzyme to bring about second-dimensional fractionation; and

(e) detecting the spots of the labeled DNA fragments fractionated in step (d) (Hayashizaki *et al.* describes method p. 256-257).

The detection step (e) is carried out using PDQUEST which is a system that scans the electrophoretic gels to produce a computer image, and thus, a genomic DNA data containing medium (section 2.3). It is noted that Hayashizaki et al. do not teach a method that is identical to the method recited in the instantly rejected claims, however, the image that is obtained by the computer, and thus the DNA data containing medium, would not be structurally different in the case of the data image that is obtained.

Claim Rejections - 35 USC § 103

13. Claims 4, 5, 6, 12, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatada *et al.* (PNAS USA, 88, p. 9523-9527) in view of Carrano *et al.* (Genomics 4, 129-136 (1989)).

This rejection applies to claims 4, 5, 6, 12, 13, and 15 when they are interpreted such that the DNA data containing medium is a gel which contain DNA fragments that were treated as recited in the claims.

Hatada *et al.* teach a genomic DNA analytical pattern which has been obtained by means of a method of analysis comprising:

(a) treating genomic DNA with a first restriction enzyme (MluI) which is capable of cutting the genomic DNA so that the 3' end of the recognition site has a protruding sticky end

(b) labeling the cleavage site

(c) treating the resulting DNA fragments with a second restriction enzyme to bring about first-dimensional fractionation

(d) treating the fractionated DNA fragments of step (c) with a third restriction enzyme to bring about second-dimensional fractionation; and

(e) detecting the spots of the labeled DNA fragments fractionated in step (d) (Hatada *et al.* describes method p. 9523, Col. 2 thru p. 9524, Col. 1).

Hatada *et al.* teach that one advantage of their method is that the scanning field of the method can be extended by the use of different kinds of landmarks (the first restriction enzyme) and further suggest the use of rare cutting enzymes (p. 9525, Col. 2). Hatada *et al.* provide examples of such enzymes, such as BssHII, an enzyme with a six nucleotide recognition site.

Hatada *et al.* provide photographs of the electrophoresis gels that are produced by their methods in Figures 2-4.

Hatada *et al.* do not teach a method for making a DNA data containing medium in which in which the labeling of step (b) is accomplished by ligating a labeled adapter to the restriction site.

Carrano et al. teach a method for labeling restriction fragments which comprises the addition of a fluorescently labeled adaptor to the end of the restriction fragment (p. 130). Carrano et al. teach "because fluorescence instead of radioactivity is measured, fragment size resolution is improved and more information may be obtained...(p. 130)" and they further teach that "the method is sufficiently universal that it can be applied to other DNA analysis schemes...(p. 136)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Hatada *et al.* by labeling the restriction fragments with labeled adaptors instead of filling in the overhangs. The ordinary practitioner would have been motivated to modify the methods of Hatada et al. in order to take advantage of the benefits of using the fluorescent adaptors taught by Carrano et al. Furthermore, with regard to claim 5, it would have been prima facie obvious to have added more than one labeled base to the adaptor, because additional labels would have increased signal intensity.

14. Claims 7, 8, and 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Hatada et al. in view of Carrano et al. as applied to claims 4, 5, 6, 12, 13, and 15 above, and further in view of the New England Biolabs Catalog (1996/1997, pages 19, 28, and 40).

The teachings of Hatada et al. in view of Carrano et al. are provided in the previous rejection. Hatada et al. do not teach genomic DNA containing mediums which were created via use of a first restriction enzyme that includes at least one "N" wherein N can be any of A, G, C, or T. However, Hatada et al. do teach that the method can be extended to the use of any other rare cutting enzymes. Furthermore, Carrano et al. teach that custom primers can be synthesized for ligating labeled adaptors to "most other" restriction ends (p. 136).

New England Biolabs provides a number of different restriction enzymes, including many rare cutters that have "N" in the recognition sequence (for example BstXI, Bg1I, and MwoI). Furthermore, New England Biolabs provides information as to whether or not the restriction enzymes are methylation sensitive.

It would have been prima facie obvious to have modified the teachings of Hatada et al. in view of Carino et al. by utilizing any of the rare cutting enzymes provided by New England

Biolabs. The ordinary practitioner would have been motivated to use alternative rare cutting enzymes by the teachings provided by Hatada et al. (who suggest extending the methods to other landmark enzymes), Carino et al. (who teach that "most other" restriction ends can be ligated to), and by New England Biolabs who provide a variety of restriction enzymes for sale via their catalog in order to provide additional methods for the study of genomic DNA.

15. Claims 4, 5, 6, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki *et al.* (Electrophoresis, 1993, 14, 251-258) in view of Carrano *et al.* (Genomics 4, 129-136 (1989)).

This rejection applies to claims 4, 5, 6, 10, and 11 when they are interpreted such that the DNA data containing medium is a gel which contain DNA fragments that were treated as recited in the claims.

Hayashizaki *et al.* teach a genomic DNA analytical pattern which has been obtained by means of a method of analysis comprising:

(a) treating genomic DNA with a first restriction enzyme that is sensitive to methylation of the genomic DNA (NotI or BssHII) which is capable of cutting the genomic DNA so that the 3' end of the recognition site has a protruding sticky end

(b) labeling the cleavage site

(c) treating the resulting DNA fragments with a second restriction enzyme to bring about first-dimensional fractionation

(d) treating the fractionated DNA fragments of step (c) with a third restriction enzyme to bring about second-dimensional fractionation; and

(e) detecting the spots of the labeled DNA fragments fractionated in step (d)

(Hayashizaki *et al.* describes method p. 256-257).

Hayashizaki *et al.* provide photographs of the electrophoresis gels that are produced by their methods in Figure 7.

Hayashizaki *et al.* do not teach a method for making a DNA data containing medium in which in which the labeling of step (b) is accomplished by ligating a labeled adapter to the restriction site.

Carrano et al. teach a method for labeling restriction fragments which comprises the addition of a fluorescently labeled adaptor to the end of the restriction fragment (p. 130). Carrano et al. teach "because fluorescence instead of radioactivity is measured, fragment size resolution is improved and more information may be obtained...(p. 130)" and they further teach that "the method is sufficiently universal that it can be applied to other DNA analysis schemes...(p. 136)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Hayashizaki *et al.* by labeling the restriction fragments with labeled adaptors instead of filling in the overhangs. The ordinary practitioner would have been motivated to modify the methods of Hayashizaki et al. in order to take advantage of the benefits of using the fluorescent adaptors taught by Carrano et al.

Response to Remarks

It is noted that Applicant did not address the request for corrected drawings set forth in the previous action. Failure to file corrected drawings in response to this office action will result in ABANDONMENT of the application.

The previous rejections under 112 2nd paragraph have been withdrawn. New rejections are set forth.

Applicant's arguments with regard to Hatada et al. in view of Deugau et al. are moot in light of the new grounds of rejection which do not rely on Deugau et al.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1655

December 11, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600